IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Li, G.L. *et al.*
Serial No.:	**10/713,424**
Filed:	November 17, 2003
Title:	IONTOPHORETIC DELIVERY OF ROTIGOTINE FOR THE TREATMENT OF PARKINSON'S DISEASE
Group Art Unit:	1617
Examiner:	D.R. Claytor
Confirmation No.:	4527
Docket No.:	**6102-000071/US**
Client Ref.:	P/Wo/IX/12/02

SUBMITTED ELECTRONICALLY VIA EFS-WEB

September 22, 2008

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE TO OFFICE ACTION DATED JUNE 25, 2008

This paper is responsive to the Office Action dated June 25, 2008 in the above referenced application, in which a shortened statutory period of three months was set for reply. This paper is timely submitted and no fee for extension of time is believed payable. However, if any fee should be found payable in respect of this submission, authorization is hereby provided to charge such fee to Deposit Account No. 08-0750.

No amendment is requested herein. Claims 2–7, 9 and 16–20 are pending in the present application. Claims 1, 8 and 10–15 were canceled by previous amendment.

1. Rejection under 35 U.S.C. §103(a)

Claims 2–7, 9 and 16–20 are rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 6,884,434 ("Müller") in view of Panchagnula *et al.* (2000) Curr. Opin. Chem. Biol. 4:468–473 ("Panchagnula") and U.S. Patent No. 6,416,503 ("Suzuki"). This rejection is respectfully traversed.

Independent Claims 5 and 9 are not obvious over the combination of Müller, Panchagnula and Suzuki at least for the reason that a person of ordinary skill would not have a reasonable expectation of successfully combining the elements of the cited documents in the fashion presently claimed. In particular, the Examiner's proposition to adapt rotigotine for use in an iontophoretic device is unsupported by the cited documents as Panchagnula illustrates that successful iontophoretic drug delivery is unpredictable. At best, Panchagnula provides an invitation to experiment, which in view of the nearly infinite variables involved, does not equate to a reasonable expectation of success. What is more, in the case of Claim 5, the combination of Müller, Panchagnula and Suzuki cannot establish a case of obviousness as the combination fails to teach or suggest at least one of the claimed features – namely triethylammonium chloride, tributylammonium chloride and combinations thereof, which the present specification shows result in high fluxes of rotigotine.

1.1. A skilled artisan would not reasonably expect that Müller and Panchagnula could be successfully combined.

The present Action combines Müller, which contains disclosure relating to a transdermal patch containing rotigotine hydrochloride for treating Parkinson's disease, with Panchagnula, which generally discloses transdermal delivery of drugs via iontophoresis. The Action, however, fails to substantiate why a person of ordinary skill would have a reasonable expectation of successfully delivering rotigotine by iontophoresis, as required by *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (a reasonable expectation of success is a required criterion for a *prima facie* case of obviousness). Obviousness does not require absolute predictability, but at least some degree of predictability is required and evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). When properly viewing the teachings of Panchagnula as a whole, including teachings of unpredictability of iontophoresis, a skilled artisan would not reasonably expect that rotigotine would be successfully delivered using iontophoresis.

Panchagnula discloses several aspects of iontophoresis that raise serious doubts as to whether any predictability exists when adapting a given drug and formulation thereof for use in an iontophoretic device. For example, skin is a complex membrane that has great influence

on the movement of molecules across it in the presence of an electric field, and this has posed an obstacle to determination of an exact relationship for iontophoretic transport (Panchagnula, p. 468, col. 2). Panchagnula further teaches that iontophoresis requires investigation on a case-by-case basis, meaning that one set of conditions cannot reasonably be expected to work for different molecules. For example, Panchagnula remarks that extensive studies need to be done with a series of small molecules and macromolecules to understand the exact role of the physico-chemical properties of penetrant in relation to iontophoretic delivery (p. 469, col. 2). Rotigotine is one such small molecule, and absent any rules establishing some benchmark of predictability, there is no way of knowing whether the drug and formulations thereof may be amenable to iontophoretic delivery. Another issue with regard to formulation is ensuring the stability of the drug under the influence of an electric field and, until now, only a few studies have been carried out on this aspect (Panchagnula, p. 472, col. 1).

It is apparent from Panchagnula that iontophoresis is not a "turn-key" delivery system and a drug cannot simply be added to a predefined system or formulation with the prospect of success. It is also notable that Panchagnula is silent as to delivery of the drug rotigotine, the use of chloride salts or any concentrations thereof in preparing drug formulations, or the pH of the composition. In this case, there is not a finite number of identified and predictable solutions that could provide reasonable expectation of success. Instead, there is merely hope and optimism that various iontophoretic products in different development stages will work for particular applications (Panchagnula, Table 1). In addition, of the nearly infinite formulation possibilities, where formulation is identified as "the crucial link between the drug and the device," there is no finite set of electrolytes, polymers, semi-solid formulations, gels, concentrations and pH identified that could provide a predictable basis for a skilled artisan to reasonably expect iontophoresis would work for rotigotine (Panchagnula, p. 470, col. 2). The unpredictability associated with iontophoretic delivery precludes a *prima facie* case of obviousness based on combining Müller and Panchagnula. Addition of Suzuki to the combination does nothing to correct this deficiency.

Failure of others is also an important secondary consideration in evaluating a case of obviousness. In particular, failed attempts of others in similar endeavors counters any reasonable expectation of successfully delivering rotigotine using an iontophoretic device and

reinforces the unpredictability in the art. For example, failed attempts to develop adequate iontophoretic systems for drugs such as apomorphine and ropinirole hydrochloride serve to illustrate the unpredictable nature of the art (see present specification as filed at p. 4, line 9 – p. 5, line 16). Failure of others is a secondary consideration pertinent to an obviousness analysis and part of the inquiry as a whole. See *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) as further sanctioned by *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) ("the [*Graham*] factors continue to define the inquiry that controls").

The nexus between the examples of apomorphine and ropinirole hydrochloride and the present case is that a skilled artisan cannot readily ascertain what chemical structures or features may be successfully incorporated into an iontophoretic system. The present invention is based in part on the surprising and unexpected iontophoretic delivery of a rotigotine composition using the recited chloride salts, concentrations and pH ranges (specification as filed, p. 6, lines 13–17; p. 7, lines 1–5 and 13–15). In view of the known failures with apomorphine and ropinirole hydrochloride, the present combination of documents cannot sustain a case of obviousness.

Unexpected results are another important *Graham* consideration in an obviousness inquiry. In the present case, studies conducted to evaluate feasibility of iontophoretic delivery of rotigotine found that the solubility of rotigotine decreases as pH is increased (specification as filed, p. 7, lines 10–12). However, it was surprisingly found that a therapeutically relevant rate was achieved at a pH of 4 to 6.5 at very low rotigotine concentrations (p. 7, lines 13–15). Thus, the present invention illustrates unexpected results in the pH range recited in the present claims that could not have been predicted by a skilled artisan in seeking to adapt an iontophoretic device for delivery of rotigotine.

1.2. The combination fails to teach triethylammonium chloride or tributylammonium chloride.

In the case of Claim 5, the cited references fail to teach triethylammonium chloride and/or tributylammonium chloride. A *prima facie* case of obviousness requires that the combined prior art references teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Or, if the references are missing claimed features,

there must be some apparent reason either in the references or the general knowledge in the art by which to modify the references to include the missing subject matter. *Id.*; *KSR. v. Teleflex, supra.* In the present rejection, Suzuki is further combined with Müller and Panchagnula for its disclosure of iontophoretic drug devices that contain sodium chloride. However, Suzuki, and the combination as a whole, is silent with respect to triethylammonium chloride and/or tributylammonium chloride.

In contrast, the present application not only teaches compositions using triethylammonium chloride and tributylammonium chloride, but also teaches that these chloride salts provide higher fluxes of rotigotine than sodium chloride (specification as filed, p. 8, lines 1–3). Prior to the present invention, there was no apparent reason for a skilled artisan to select triethylammonium chloride and/or tributylammonium chloride in place of sodium chloride. The combination of Müller, Panchagnula and Suzuki therefore fails to teach the particular chloride salts recited in Claim 5, and further fails to appreciate any benefit, advantage, or even suitability of including these particular chloride salts in place of sodium chloride. And no reason based on the general knowledge in the art has been articulated to insert the missing subject matter.

The present Action alleges that "[d]ue to Applicant's own admission in the specification spanning the last paragraph of page 7 to page 8, any pharmaceutically acceptable chloride salt can be used in the invention and teaches equivalency of NaCl, triethylammonium chloride and tributylammonium chloride which would lead one of ordinary skill in the art to believe that any of the 3 above mentioned chloride salts are equivalent and can be used in the invention" (Action, p. 5).

First, Applicant has made no such admission as to the alleged equivalence of triethylammonium and tributylammonium chlorides to NaCl. Indeed, the cited paragraph explicitly states that triethylammonium and tributylammonium chlorides are preferred over NaCl because they result in higher fluxes of rotigotine. This is a statement of non-equivalence. (NaCl does work, only not as well as the salts recited in Claim 5.)

Second, the Examiner's reasoning amounts to impermissible use of hindsight as it is entirely and admittedly predicated on Applicant's disclosure. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971) (an obviousness inquiry cannot include knowledge

gleaned only from applicant's disclosure). As Applicant's disclosure cannot form the basis for a case of obviousness, there is no apparent reason to modify the combination of Müller, Panchagnula and Suzuki to include triethylammonium chloride and/or tributylammonium chloride, as recited in Claim 5.

2. Conclusion

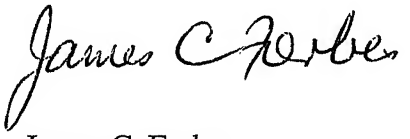
For reasons set forth above, Claims 5 and 9 are non-obvious over the cited combination of Müller, Panchagnula and Suzuki. Claims 2–4, 6 and 7 depend directly or ultimately from and incorporate all limitations of Claim 9, and are therefore non-obvious for at least the same reasons that Claim 9 is non-obvious. Claims 16–20 depend directly or ultimately from and incorporate all limitations of Claim 5, and are therefore non-obvious for at least the same reasons that Claim 5 is non-obvious. Withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested.

It is believed that all of the stated grounds of rejection are properly traversed, accommodated or rendered moot herein. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.

Respectfully submitted,

HARNESS, DICKEY & PIERCE, P.L.C.



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